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Title: First Study of Safety and Tolerability of MDMA-Assisted Psychotherapy in Patients with Alcohol Use Disorder

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Abstract:

Background: MDMA therapy has qualities that make it potentially well-suited for patients with addictions (Sessa 2017), but this has never been explored in a research study. We present data from the Bristol-Imperial-MDMA-for-Alcoholism (BIMA) study. This is the first MDMA addictions study; an open-label safety and tolerability proof-of-concept study investigating the potential role for MDMA therapy in treating patients with Alcohol Use Disorder (AUD).

Aims: To assess if MDMA-Assisted Psychotherapy can be delivered safely and can be tolerated by patients with AUD post-detoxification. Outcomes regarding drinking behaviour, quality of life and psychosocial functioning were evaluated.

Methods: 14 patients with AUD completed a community alcohol detoxification and received an 8-week course of recovery-based therapy. Participants received two sessions with MDMA (187.5mg each session). Psychological support was provided before, during and after each session. Safety and tolerability were assessed alongside psychological and physiological outcome measures. Alcohol use behaviour, mental wellbeing and functioning data were collected for 9-months after alcohol detoxification.

Results: MDMA treatment was well-tolerated by all participants. No unexpected adverse events were observed. Psychosocial functioning improved across the cohort. Regarding alcohol use, at 9-months post-detox the average units of alcohol consumption by participants was 18.7 units/week, compared with 130.6 unit/week pre-detox. This compares favourably to a previous observational study (the 'Outcomes' study) by the same team with a similar population of people with AUD (Sessa et al 2020).

Conclusions: This study provides preliminary support for the safety and tolerability of a novel intervention for AUD post-detox. Further trials to better examine the therapeutic potential of this approach are now indicated.

Introduction

Alcohol Use Disorder: Drinking is a socially acceptable behaviour and the majority of people consume alcohol without significant problems, but a growing number drink in a harmful manner. Alcohol Use Disorder (AUD), (DSM-5, APA 2013) encompasses a broad spectrum of clinical presentations related to harm associated with alcohol use. Approximately 24% of the adult population of England consume alcohol harmfully, with about 6% of men and 2% of women meeting criteria for alcohol physical dependence. AUD is characterised by often serious withdrawal symptoms on cessation of alcohol, drinking to avoid withdrawal symptoms, tolerance, the persistent desire to drink and continuing drinking despite negative consequences (NICE guidelines on Alcohol Use Disorders, 2011). The impact of alcohol misuse is widespread; encompassing alcohol-related illness and injuries as well as significant social impacts to family, friends and the wider community. Patients with AUD frequently have a past history of psychological trauma and commonly present with high levels of depression, social anxiety and social exclusion, having become dependent upon alcohol as a form of self-medication (Castillo-Carniglia et al 2019). And in the context of the current Covid 19 pandemic, attention to the issue of best management of AUD has become even more pertinent (Clay & Parker 2020).

Traditional treatments for AUD include medical and psychosocial interventions. Pharmacological options include acamprosate, naltrexone, nalmefene and disulfiram, which reduce cravings and deter relapse respectively (Rösner et al 2010, Soyka & Rösner 2008, Paille & Martini 2014, Krampe et al 2006). Benzodiazepines are commonly prescribed as part of alcohol detoxification programmes (Lingford-Hughes et al 2012). Large-scale studies of psychosocial interventions have emphasised the importance of psychotherapies and non-pharmacological supports (Miller and Wilbourne 2002, Project MATCH Research Group

1997a, Anton et al., 2006, UKATT Research Team 2005). In recent years, Mindfulness techniques have been increasingly explored as a potential approach to assist recovery through interrupting the tendency to respond to stress with alcohol use and not to react automatically to cravings (Marcus and Zgierska 2009).

MDMA: MDMA is a phenethylamine that raises levels of monoamine neurotransmitters in the brain. MDMA elevates mood, increases sociability and feelings of closeness to others, and can facilitate imagination and memory (Sessa, Higbed & Nutt 2019). Evidence from neuroimaging studies show a decrease in amygdala/hippocampus activity (Carhart-Harris et al (2014) and an association between reduced amygdala activity and improved ability to process negative memories. (Carhart-Harris et al 2013). Together with changes in social cognition, interpersonal closeness and communication, these data support the proposition that MDMA could be of benefit as an adjunctive psychotherapeutic treatment for alcohol addiction and comorbid psychological disorders (Sessa 2017). The use of MDMA-assisted psychotherapy to manage PTSD has been explored since the 1980s (Greer 1998). More recently, long term follow-up data from the first completed trial of MDMA-assisted psychotherapy for chronic, treatment-resistant PTSD has found statistically and clinically- significant gains in symptom relief with no subjects reporting harm from participation in the study (Mithoefer *et al* 2010; Mithoefer *et al* 2013). The US-based research group, the Multidisciplinary Association for Psychedelic Studies (MAPS), have published favourable results of their phase 2 studies (Mithoefer et al 2019). MAPS is now in the Phase 3 stage of medicine development, with anticipated licensing and FDA approval in the USA in late 2022 to early 2023. European approval by EMA is anticipated in 2023.

The potential risks associated with MDMA as an adjunct to psychotherapy: Rarely, users of clinical MDMA experience an increase in anxiety associated with derealisation-type

experiences (Mithoefer et al 2010). Acute neurocognitive effects include a transient reduction in verbal and visual memory, which tend to resolve after the drug has worn off (Kuypers 2007). MDMA misuse potential needs to be borne in mind when proposing giving the drug to a population with pre-existing addiction issues. However, in the studies in which MDMA has been administered clinically in a therapeutic setting to healthy volunteers without any previous experience with ecstasy, subjects did not express a wish to use it outside of the clinical setting (Mithoefer 2013). Taken together, these findings suggest that clinically administered MDMA is not likely to produce problematic use (Jerome et al 2013). In order to monitor the risk of patients using MDMA outside of the study, we monitored their use or desire to use illicit ecstasy with specific questions pertaining to this issue asked in the final (session 10) therapy session.

Clinical MDMA increases blood pressure, heart rate and body temperature (Harris et al 2002) and causes jaw tightness, bruxism, reduced appetite, poor concentration and impaired balance (Mithoefer 2010). Despite historical reports of neurocognitive deficits in recreational ecstasy users, contemporary studies have failed to demonstrate any significant long-term neurotoxicity associated with recreational ecstasy when use of other recreational drugs is controlled for (Hanson & Luciana, 2010, Selvaraj 2009). There have been no reports of long-term neurotoxicity or neurocognitive impairments when pure MDMA has been administered in a controlled clinical setting (Mithoefer 2013).

Methods

Approvals and drug source: This trial, sponsored and approved by Imperial College London, received a favourable opinion from the Central Bristol Research Ethics Committee of the National Research Ethics Service and from the Medicines and Healthcare products Regulatory Agency. A Home Office License for storage and dispensing of Schedule One drugs was

obtained. GMP MDMA was obtained from Sterling Pharmaceuticals (Newcastle) and formulated into the investigational medicinal product (62.5mg MDMA in gelatine capsules) by Guy's and St Thomas' Hospital's Pharmacy Manufacturing Unit (London, UK).

Study design: This was an open label within-subject safety and tolerability feasibility study, in 14 patients aged 18 to 65 with AUD who had recently undergone detoxification. All patients received MDMA-Assisted therapy. The main outcome measures were the number of patients completing the 8-week psychotherapy course, the number accepting the second booster dose of MDMA on drug assisted days and adverse events. Secondary outcome measures included changes in drinking behaviour (measured by 'units per week consumed' at 3-, 6- and 9-months since completion of detoxification), measures of mental wellbeing, psycho-social functioning, quality of life and concomitant drug use.

Patients with a primary diagnosis of AUD who were seeking detoxification – with or without medical assistance - were recruited from the North Somerset Substance Misuse Service ('*Addaction'*). Patients received an eight-week course of recovery-based therapy comprising 10 psychotherapy sessions. On two of these (session 3 and session 7) patients were dosed with open-label MDMA during a 6-8 hour assisted therapy session. On each dosing session, participants received an initial oral dose of 125mg MDMA, followed two-hours later by a booster dose of 62.5mg MDMA. The booster dose served to prolong the experience, allowing for greater time for psychotherapy under the influence of the drug.

Other sessions (1, 2, 4, 5, 6, 8-10) comprised 1-hour psychotherapy sessions, employing aspects of Motivational Interviewing and 'third wave' cognitive-behavioural approaches. Patients remained in the study for a duration of approximately 10-months.

Trial procedures

The inclusion and exclusion criteria were as follows:

Inclusion Criteria

- Informed consent
- Primary diagnosis (as defined by DSM-5) of alcohol use disorder.
- Successful alcohol detoxification (no longer consuming any alcoholic substances).
- Between 18 and 65 years old.
- Be able to identify in advance a supportive significant other(s) who could accompany the patient to study visits if required and be contacted by the study team in the event that the patient themselves cannot be contacted.
- Proficient in speaking and reading English.
- Agree to comply with requirements of protocol.

Exclusion Criteria

- Lacking capacity
- History of, or a current, primary psychotic disorder, bipolar affective disorder type 1 or personality disorder.
- Present a serious suicide risk; as determined by the Columbia-Suicide Severity Risk Scale (C-SSRS).
- Relevant abnormal clinical findings at screening visit judged by the investigator to render subject unsuitable for study. Including but not limited to a history of cardiac disease, hypertension and stroke, severe liver disease, history of epilepsy, istory of Malignant Hyperthermia (Central Core Disease)
- Regular user of Ecstasy (material represented as containing MDMA). E.g. more than five times in the last five years or at least twice in the 6 months prior to the start of the study.

- Currently taking or unwilling/unable to stop any medications likely to interact with MDMA the opinion of the investigators, during 8 week MDMA assisted therapy.
- Regular use of/dependence on other drugs such as benzodiazepines, synthetic cannabinoids, cocaine and heroin.
- For females of childbearing age/potential, articipants must use an effective form of birth control for at least six days after administration of MDMA, and must not be pregnant and/or breast-feeding, until the end of the treatment phase.
- For males with partners of childbearing age/potential, participants must themselves confirm use of an effective form of birth control for at least six days after administration of MDMA and confirm their partner will also.
- Taken part in a study involving an investigational product in the last three months
- Patients that might face additional risks from immunosuppression (for example patients with immunological diseases, patients with active infection or history of infections within 4 weeks of MDMA administration).

AUD was identified using the DSM-IV SCID interview. Screening comprised of written informed consent, an evaluation of the patient's physical and mental health background, a psychiatric interview (MINI), assessments of depression and anxiety severity were assessed using the PHQ-9 and GAD-7 questionnaires. Severity of AUD was established using the SADQ and SIP questionnaires. Patients received a thorough physical health check comprising of an electrocardiogram (ECG), routine blood tests, blood pressure, heart rate, and physical examination. Following screening, eligible patients underwent the process of detoxification; either by gradually cutting down alcohol consumption over many weeks, or with a medically-assisted detoxification regime. The majority of participants were also taking medications for anxiety and/or depressive symptoms, e.g. SSRIs. According to the inclusion/exclusion criteria,

associated medications that are known to attenuate the effects of MDMA were subsequently gradually reduced and stopped under medical supervision, ahead of the first MDMA session. A further 'baseline' visit clarified successful detoxification using the CIWA questionnaire before eligible participants entered the 8-week course of psychotherapy. This entailed weekly 60-minute outpatient non-drug psychotherapy sessions, delivered by two clinicians (BS and LH), trained in delivering MDMA-assisted psychotherapy by the USA based organisation, MAPS.

Dosing with MDMA occurred twice during the 8-week course; on weeks 3 and 6. Physiological changes, observer and subject ratings of distress (SUDS) and the intensity of MDMA's acute psychoactive effects were measured throughout the drug-assisted session. Acute anxiety was managed primarily psychologically, but sedative medication (oral lorazepam) was available. Participants remained overnight in the treatment centre after each drug-assisted session, overseen by medically-trained 'night sitters', on hand to support participants as required but instructed to avoid delivering any psychotherapeutic interventions.

Participants were seen the morning after each drug-assisted session for an integration psychotherapy session, and then telephoned daily for six days to assess changes to mood, suicidal risk factors (using C-SSRS) and quality of sleep (using the Leeds Sleep questionnaire). Following the end of the 8-week therapeutic course participants carried out additional follow-up questionnaires. They were then seen again at 3-, 6- and 9-months (since baseline) for longer-term follow-up data collection.

Data analysis

All data were recorded on paper CRF's and then digitized into MS Excel spreadsheets. Analysis and graphing were performed using GraphPad (Prism) or MS Excel. As this is a non-RTC, open label study, no hypothesis testing was performed. When calculating Timeline Follow

Back results, alcohol consumption levels at last observation were used in the case of drop-outs or when participants had undertaken a second detoxification (Hamer and Simpson, 2009).

Results

Demographics:

- 36 participants attended face-to-face screening visits.
- 14 were enrolled; 8 males and 6 females; average age 48 years.
- All were White British.
- 4 were employed, 9 unemployed and 1 was retired.
- The average age of first alcohol use was 13 years-old.
- The average age when alcohol became problematic was 34 years-old.
- 64% of participants reported a history of alcohol-related blackouts, 14% had experienced alcohol withdrawal-induced seizures, 86% of participants reported having experienced risky or vulnerable incidences due to alcohol and 75% of participants had had forensic / offending behaviour secondary to their alcohol use.

Severity of AUD criteria at screening and baseline: As per the inclusion criteria, all eligible patients scored above the diagnostic threshold on the DSM-5 SCID questionnaire for AUD. We also measured AUD severity using the SIP questionnaire and the SADQ questionnaire (figure 1), with most eligible participants in the moderate to severe range. At the point of Baseline visit, (within one week of detox completion), 100% of eligible participants had successfully completed detoxification, assessed using the CIWA scale.

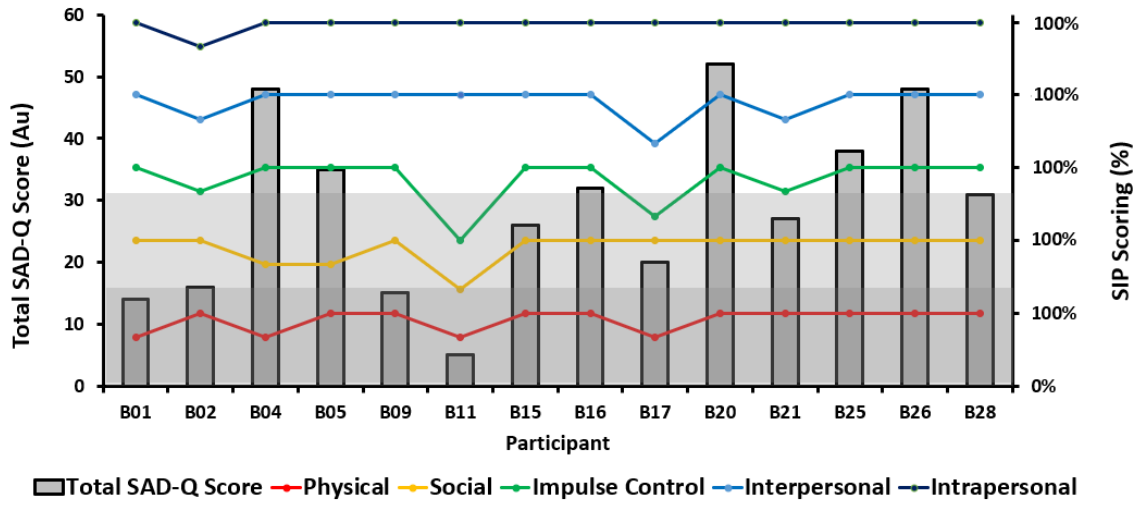

Figure 1. Severity of Alcohol Questionnaire (SADQ) measures alcohol dependency (Au = arbitrary units). Short Inventory of Problems for Alcohol (SIP) is a 15-question measure of self-noted consequences of drinking. Both observed at screening. SIP categories are separated each between 0-100% on the second y-axis. A score of 31 or higher indicates severe alcohol use disorder severity, a score of 16-30 indicates moderate alcohol use disorder severity (light grey area), anything lower than 16 indicates mild alcohol use disorder severity (dark grey area). 4 SADQ questions were unanswered, in which case, mean substitution was applied using the average row value for the relevant time period and participant. B05, B16, B20 and B21 had one question missing each.

Physiological and Tolerability Effects during MDMA sessions: Twelve of the fourteen participants received both sessions of MDMA-assisted psychotherapy. So, in total, 26 drug-assisted psychotherapy sessions with MDMA were administered during the trial. Temperature, blood pressure and heart rate were measured at t=0, before taking the medicine, then half-hourly up to t=2 hours, then hourly thereafter for a minimum of 6-hours from the time of dosing (figure 2).

Except for one participant, all of these physiological parameters remained within normal limits for all these sessions. As expected, we saw a mild, transient rise on blood pressure, temperature and heart rate over the course of the MDMA session. No patients experienced sustained abnormal physiological disturbance, symptomatic experiences of raised blood pressure, heart rate or temperature or any other adverse events during MDMA sessions. No medical interventions were required in respect of these or any other physiological events during MDMA

sessions. One participant experienced a transient abnormal rise in blood pressure after taking the initial dose of 125mg MDMA reaching a BP 183/118 at 2-hours after dosing, attributed to the participant forgetting to take her regular antihypertensive medication on the morning of dosing. Although she was asymptomatic and no medical intervention was required it was decided to withhold the 2-hour supplemental dose. Her blood pressure subsequently spontaneously returned to normal in the following two hours and she agreed with the study team to omit the booster dose of MDMA on that day. She did, however, receive her second MDMA session three weeks later, (after taking her antihypertensive medication in advance appropriately), which was uneventful in terms of blood pressure. Another participant only received their first session with MDMA. She subsequently relapsed back to heavy drinking in the context of personal psychosocial issues unconnected with the study, and therefore chose to not have her second MDMA session.

Subjective Units of Distress (SUDS) and Participant report of Drug Effects were also measured, hourly, throughout the MDMA sessions (figure 3). Most subjects predictably reported mildly raised SUDS scores at the beginning of the sessions before taking MDMA – consistent with expected anxiety ahead of dosing – which subsequently reduced during the course of the session as the positive effects of MDMA emerged. Participants gave their own subjective score (0-10) of whether they felt Drug Effects, and the therapists also recorded their own objective score of how 'altered' the participant appeared. There was no significant difference between Observers' and Participants' Drug Effects scores. Drug Effects rose expectedly over the first 2-hours, with a notable further increase after the booster dose was given at t=2 hours, and a subsequent plateau then decline over the following six hours. By the end of the MDMA session day all drug effects had returned to baseline. No participants reported any significant neurocognitive impairments associated with receiving MDMA in the weeks and months following participation in the study.

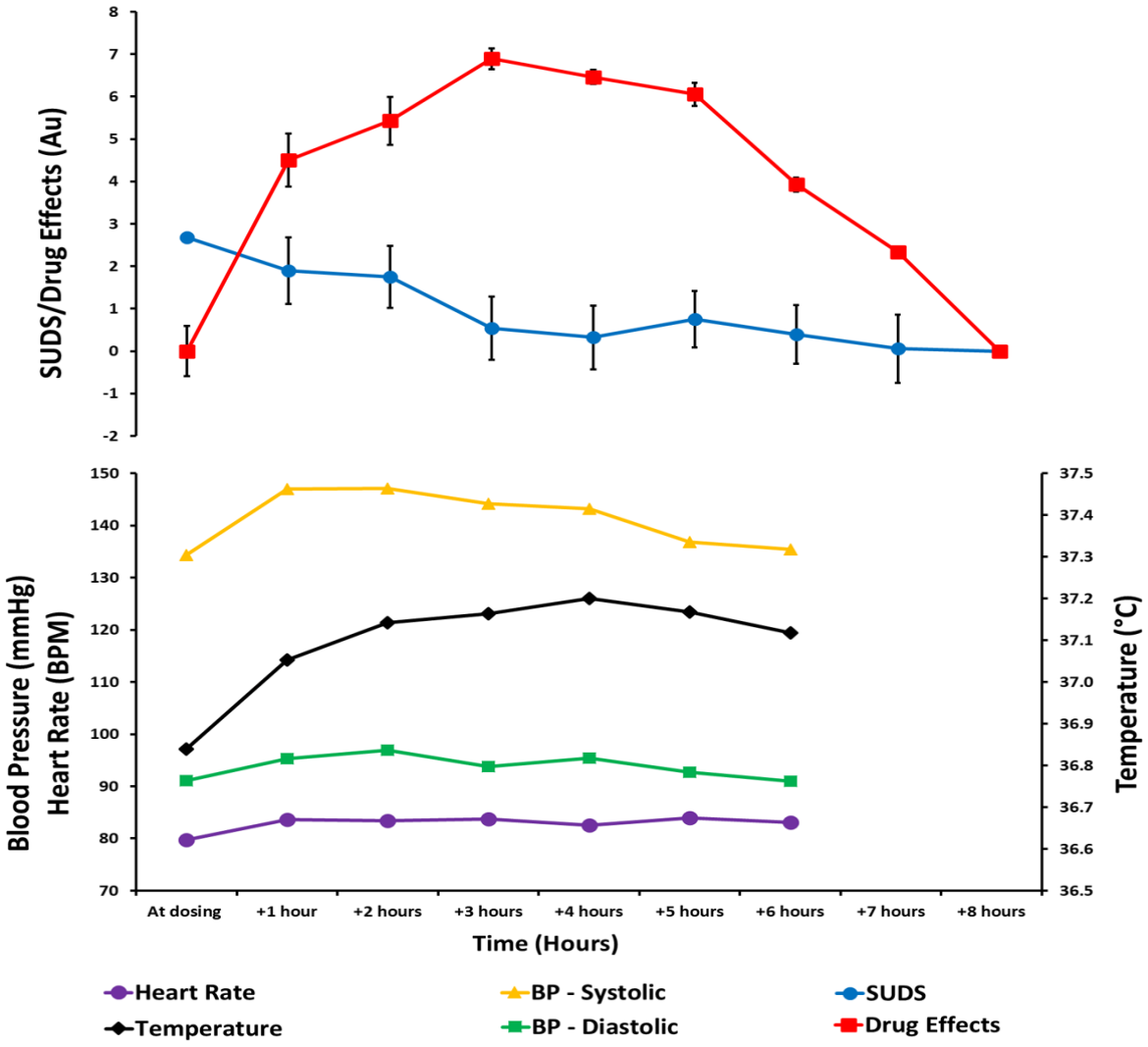

Figure 2. Pooled data of Blood Pressure, Temperature, Heart Rate, Observed Drug Effects and Subjective Units of Distress (SUDS) observed over the duration of the MDMA sessions. SUDS and Drug Effects observed over 8 hours, physiological data observed over 6 hours following dosing. Mean data for each session is used, except in the case of missing data, where available session data is applied. Error bars (where applied) indicate +/- SEM.

Changes in Drinking Behaviour: Whilst changes in drinking behaviour were not a primary outcome measure, we nevertheless collected data in respect of Units of Alcohol Consumed per Week in the month before participants' detoxification, immediately after detox ('Baseline'), throughout the 8-week MDMA therapy course and for up to 9-months after detox. Of the n=14 eligible participants who underwent the course of MDMA-assisted psychotherapy, at nine-months follow-up endpoint, 11 participants were drinking less than 14 units of alcohol/week (including 9 who were totally abstinent from alcohol) and 3 participants had relapsed to

drinking over 14 units of alcohol/week. On average participants were drinking 130.6 units of alcohol / week in the month before detoxification, zero at the point of detox, and at the end of 9-months the average amount of consumed alcohol had risen back to 18.7 units / week (figure 3).

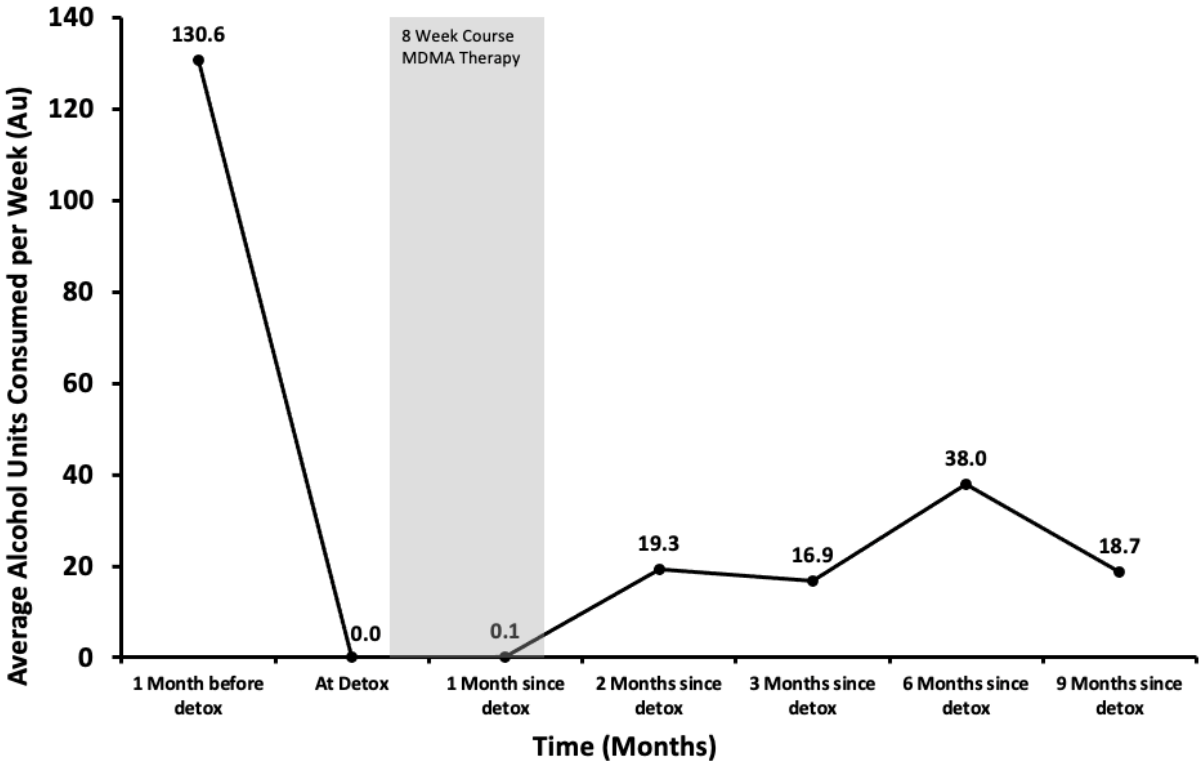

Figure 3. Timeline Follow Back (TLFB), assesses drinking behaviour prior to, and following the study. Data is collected daily by self-reporting and reviewed at 1 month prior to detox, immediately following detox and at 1, 3, 6, and 9 months follow-up. A full dataset was not available for 3 of the participants. One participant dropped out of the study at 3-months and two patients failed to provide data at 9-month follow-up. Two participants had a second detoxes since starting the study. For these participants, TLFB drinking behaviour data was carried forward from the point of drinking levels pre-second detox.

Seven-Day Follow-Up after MDMA sessions: Considerable medical and popular press literature reports the anecdotal observation of ecstasy users experiencing an acute 'come down' effect and a drop in mood in the days after using the drug recreationally. In order to measure this prospectively with clinical MDMA, we measured participants' mood states by daily Profile Of Mood States (POMS) measurements for 7-days after each MDMA session. (figure 4). Positive scores represent depressed affect, zero represents no change in mood/affect and results

below zero represent a positively felt mood. Average scores across both MDMA sessions for all 14 participants (26 MDMA sessions) reveal no evidence of any mood disturbance during the week after taking each session of clinical MDMA. Indeed, participants sustained a positive mood for 7-days. This result contrasts with anecdotal reports from recreational ecstasy users.

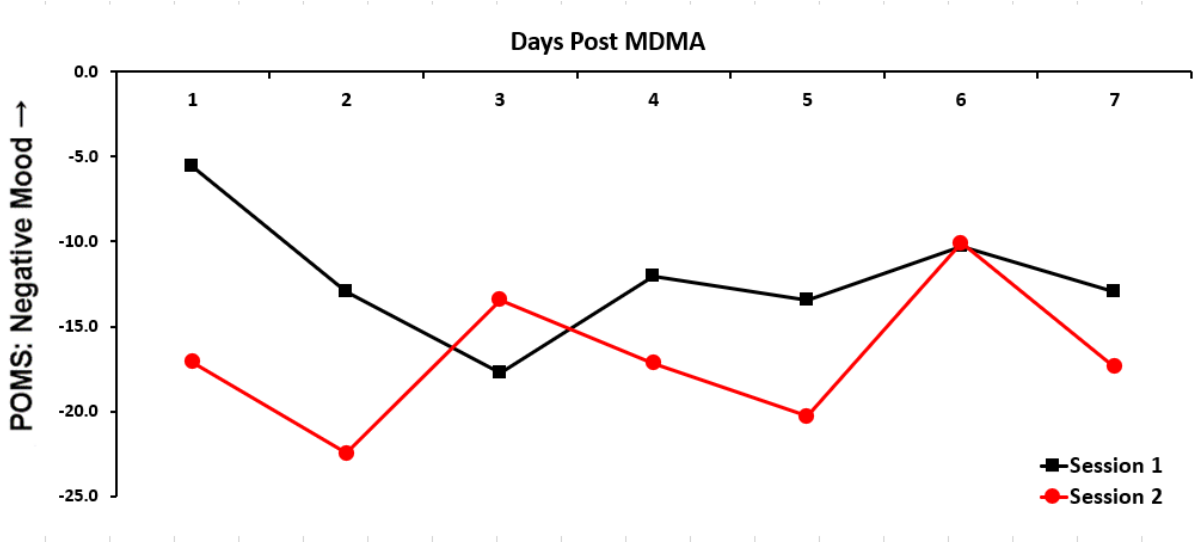

Figure 4. Profile of Mood States (POMS), individual composite scores of mood disturbance observed daily over a week following dosing. Mean data shown for both MDMA sessions. In the case of absent data for either session the available data for the remaining session is used.

Other Mental Health Measures and Quality of life measures: Brief assessments of mood and anxiety were made at screening, baseline, after the 8-week MDMA Therapy course and at 3,6 and 9-month follow-ups, using the PHQ-9 and GAD-7 rating scales respectively (figure 5). Scores demonstrate a reduction in both anxiety and depression after screening and baseline timepoints, followed by a transient rise in anxiety and depression scores 3-months after baseline and a further reduction at 6-month and a moderate rise again at 9-months post detox.

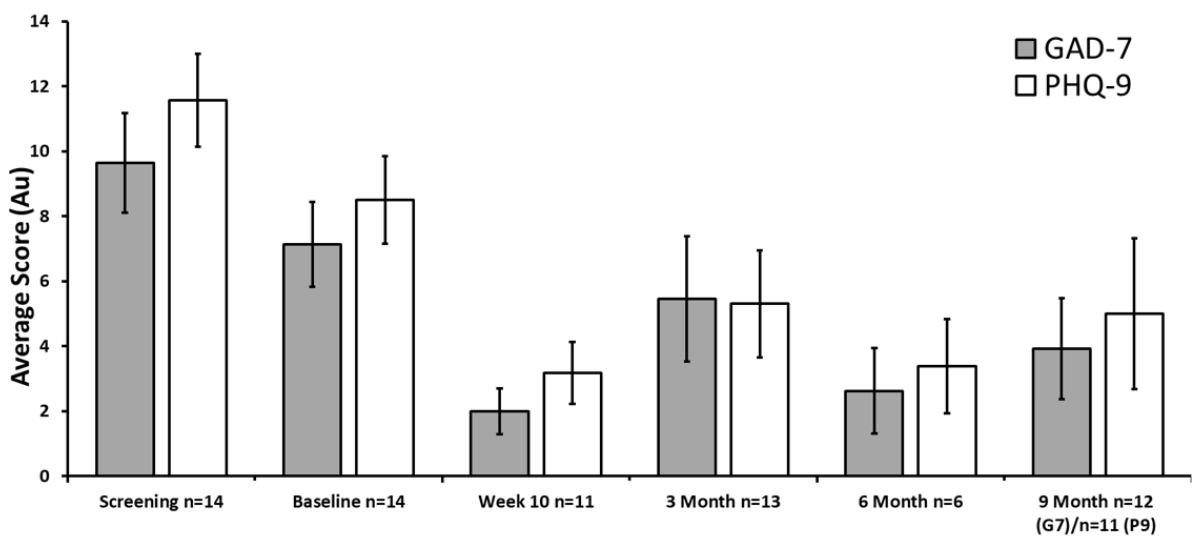

Figure 5. General Anxiety Disorder 7 (GAD-7) and Patient Health Questionnaire 9 (PHQ-9). Self-report scales for anxiety and depression (respectively). Recorded at screening, baseline, week 10, then 3, 6, and 9 months follow-up. Greater scores report indication of heightened anxiety/depression. Error bars indicate +/- SEM.

Suicidality: Participants underwent the C-SSRS rating scale at screening, baseline, throughout the 8-week therapy course, in the week after each MDMA session and at 3-, 6- and 9-month follow-up visits. No participants reported current suicidal ideation, intent or plans or self-harm behaviour during the course of the study

Adverse Events: The acute effects of MDMA-assisted psychotherapy were well-tolerated by participants. No unexpected adverse events occurred. No participants reported any desire to use illicit ecstasy / illicit MDMA following receiving clinical MDMA as part of this trial. No psychotic symptoms were observed in any of the patients.

A variety of further data were collected, including changes to the quality of sleep, quality of life measures and changes to compassion and empathy scales, which will be published in forthcoming papers.

Discussion

In this first safety and tolerability study, we demonstrate that MDMA-assisted psychotherapy could be useful in treating AUD, probably through its capacity to enhance the

psychotherapeutic process or indirectly through augmenting the treatment of co-morbid psychological conditions commonly associated with alcohol use disorder (Jerome et al 2013).

The capacity for MDMA to increase feelings of empathy and compassion for the self and others may contribute to improved self-awareness and subsequently reduce the denial of harmful use of alcohol. Recreational MDMA users have reported improved intrapersonal attitudes and pro-social attitudes towards the self, which could be a mechanism by which the drug enhances psychotherapy, especially for patients with pre-existing histories of trauma (Stolaroff 2004). Similarly, Mithoefer (2010) described MDMA's capacity to "*make yourself present in the moment*"; a core concept of mindfulness. Drug-assisted psychotherapies with the 'classic' psychedelic compounds LSD and psilocybin utilise the induced subjective mystical / spiritual effects of the psychedelic experience and have found the depth of this experience is strongly associated with maintained recovery from harmful substance use (Sessa & Johnson 2015). However, not all patients are able or willing to tolerate the classic psychedelic experience, and compliance is a critical aspect of addiction therapy. Whilst there is also an, albeit minimal, subjective spiritual / mystical experience associated with MDMA (Sumnall et al, 2006), it is generally better tolerated than the classic psychedelics, with less perceptually disturbing effects compared to LSD and psilocybin. Therefore, MDMA offers an alternative opportunity for enhanced psychotherapy in patients with AUD.

Prior to carrying out the BIMA study, the same study team carried out a non-interventional observational study, following n=14 participants through their treatment-as-usual post-alcohol detox (the 'Outcomes Study') (Sessa et al 2020). The eligibility criteria and questionnaires used in the Outcomes Study were similar to the BIMA study, in respect of assessment of AUD, severity of AUD, success of detoxification and follow-up of outcomes in respect of mental health issues and drinking behaviours – measured at 3,6 and 9-months post-detox, but without

the additional 8-week therapeutic course with MDMA-assisted psychotherapy, which occurred post-detox. Whilst it is not appropriate to statistically compare these two studies – as patients were not randomised into the studies - the graph below demonstrates the success of BIMA participants in terms of alcohol consumption over 9 months, compared with current best treatments available locally. Only 21% of participants who had undergone MDMA-assisted psychotherapy were drinking in excess of 14 units of alcohol a week in comparison with the 75% observed in the Outcomes Study (figure 6).

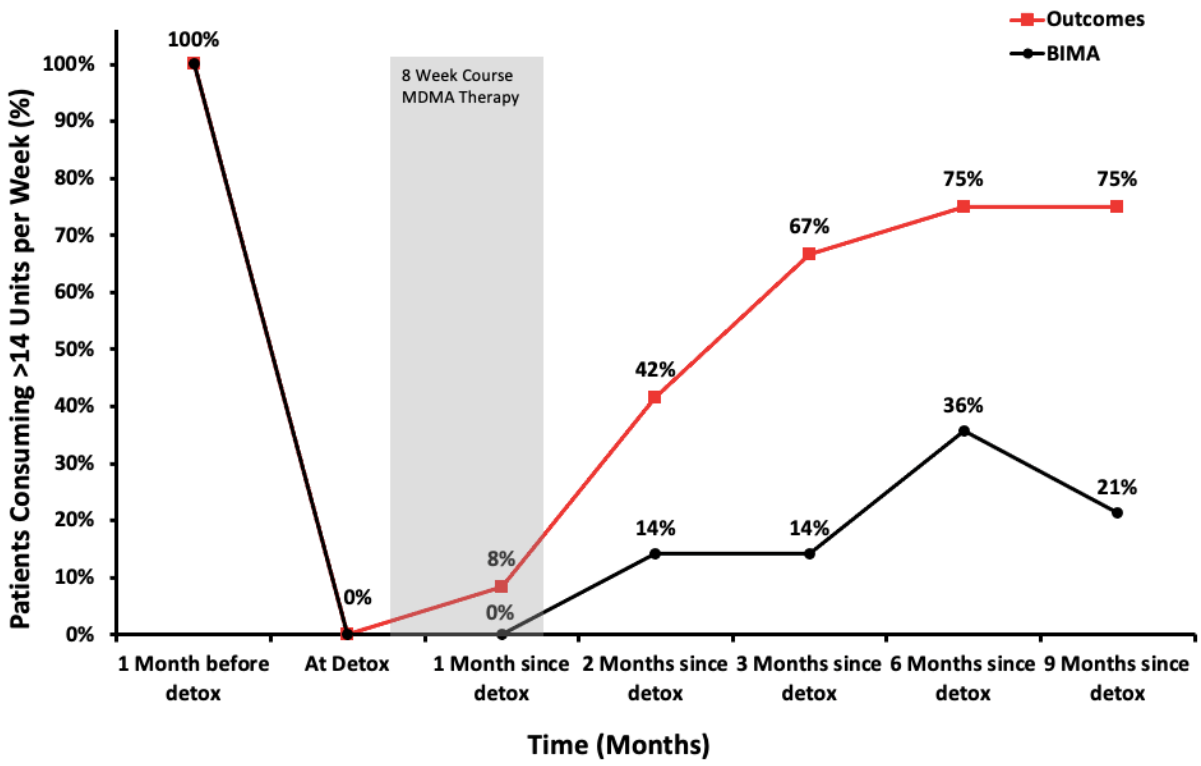

Figure 6. TLFB showing % of patients consuming more than the 14 recommended daily units of alcohol (Sessa et al 2020).

Limitations: The BIMA study had a relatively small sample size. As directed by the Medicines and Healthcare products Regulatory Agency (MHRA), given that the study was exploring a first-time drug intervention in a previously unexplored clinical population, it was

an open-label, non-placebo-controlled study. Therefore all patients knew they would be getting MDMA. Whilst efforts were made to test objectively for alcohol use using regular breath alcohol analysis, review of participants' medical notes throughout the study and carrying out Gamma-GT blood tests post-course, all data represented above were nonetheless reliant primarily on retrospective self-report. The study team considered other techniques to objectively assess alcohol use, such as worn alcohol sweat meters, but given that efficacy (drinking outcome) was not a primary outcome measure this was concluded to be overly intrusive for this type of study.

Conclusion:

In summary, this study demonstrates that MDMA-assisted psychotherapy can be safely delivered, is well tolerated and has the potential to enhance and intensify the psychotherapeutic processes in the treatment of patients with AUD. MDMA, given in a psychotherapeutic context, may reduce avoidance of emotionally distressing thoughts, images or memories of alcohol misuse while increasing empathy for the self and others. It may also address symptoms of other conditions that are frequently comorbid with harmful use of substances, particularly those symptoms associated with a history of psychological trauma.

A logical next-step would be to carry out a placebo-controlled RCT in which the level of therapist-contact is consistent between conditions. This would enable any between-group differences in clinical outcomes to be attributed to MDMA rather than the psychological support provided.

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Research in context: Evidence before this study: The database Pubmed was searched up until the 30th April 2016, using the terms "MDMA", "alcohol use disorder", "alcoholism" and "addictions". We did not find any clinical trials assessing MDMA as a treatment for alcohol use disorder – or any other substance use addiction. We found just one editorial proposing the theoretical potential for MDMA-assisted psychotherapy in the treatment of addictions (Jerome et al 2013). There have been scant animal studies on the subject. In one study, two strains of rats who had been previously conditioned to show a preference for alcohol showed an attenuation of alcohol use after administration with MDMA (Rezvani 1992).

Added value of this research: To our knowledge, this is the first investigation of the safety and tolerability of MDMA-assisted psychotherapy as a treatment for AUD. Our findings demonstrate that MDMA-assisted psychotherapy is feasible, safe and may have value as a treatment option in the management of AUD. Both sessions of MDMA-assisted psychotherapy, with doses of 187.5mg (in split doses each session) were well-tolerated and led to enduring reductions in symptom severity, sustained for 9-months in the majority of participants.

Implications of all the available evidence: The results of this small-scale safety and tolerability study should help motivate further research into the efficacy of MDMA-assisted psychotherapy with psychological support for alcohol use disorder. Larger-scale RCTs are warranted to better examine the potential of MDMA-assisted psychotherapy as a treatment option for this highly prevalent, disabling, costly and difficult to treat disorder. More broadly, the present study should help to catalyse the re-emergence of MDMA facilitated psychotherapy as a promising mental health research area.

Declaration of Interests: None

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